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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/353,126	07/14/99	MALINOW R	CSHL.005.01U

HM22/1012

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EXAMINER	
TURNER,S	
ART UNIT	**PAPER NUMBER**
1647	3

DATE MAILED: 10/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

US GPO 2000, 465-188/25266

Office Action Summary

Application No.	Applicant(s)
09/353,126	Malinow et al.
Examiner	**Group Art Unit**
Sharon L. Turner, Ph.D.	1647

☒ Responsive to communication(s) filed on 6-5-00

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-12 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-12 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Information Disclosure Statement

1. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Double Patenting

2. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

3. Claims 1-12 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12 of copending Application No. 09/193,221. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Applicants were notified on 9-6-00 that claims 1-12 in instant application are identical to those of the '221 application. However, no preliminary amendment has yet been received to correct the overlapping subject matter.

Claim Rejections - 35 USC § 112 first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claimed invention is drawn to methods for screening for drugs for the treatment of Alzheimer's Disease comprising "contacting mutant hippocampal cells having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug". One skilled in the art recognizes that it would require undue experimentation to practice the invention drawn to methods for screening for drugs given that claimed "mutant hippocampal cells" encompass hippocampal cells with any number of a myriad of mutations, e.g. mutations in a presenilin gene, as encompassed by the claims. One skilled in the art recognizes that modification of nucleotide sequence elements as claimed, e.g. mutations in a presenilin gene, produces nucleotide sequences that mediate unpredictable effects on gene function, for example unpredictable effects on regulation of expression of the genes operably linked to promoter region. For example, in view of the teachings of Smith et al (see PTO-892) and Darnell et al (see PTO-892) that modification of nucleotide sequences, for example by substitutions or other mutations including alterations of the reading frame, initiation codon, stop codon, and/or alignment of exons, produces nucleotide sequences that mediate unpredictable effects with regard to biological function of the mutated gene, e.g cellular synaptic function, one skilled in the art recognizes that

the specification does not enable one skilled in the art to reliably and reproducibly predict the function, e.g synaptic function, of "mutant hippocampal cells" in view that mutations mediate unpredictable effects on biological function. Further, the above teachings indicate that the ability of one skilled in the art to ascertain/assess the effects of "screening for drugs for the treatment of Alzheimer's Disease" is unpredictable given that even a single gene mutation can alter the biological function of claimed hippocampal cells in an unpredictable manner. One skilled in the art would require undue experimentation to predictably ascertain the effects of drugs in methods to determine "activity of a candidate drug for the treatment of Alzheimer's Disease" as claimed.

Further, in view of the teachings of Parent et al (see PTO-892), one skilled in the art recognizes that the claimed invention, drawn to methods for screening for drugs for the treatment of Alzheimer's Disease comprising "contacting mutant hippocampal cells having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug", is unpredictable given that Parent et al teach results that are contradictory to the claimed invention (see below). In particular, Parent et al teach that, upon stimulation of mutant hippocampal cells (i.e. mutant hippocampal cells produced by a mutation in a presenilin gene) by stimulation with a tetanic stimulus (i.e. either theta-burst tetanic stimulation or high-frequency tetanic stimulation), no differences were observed, i.e. differences with regard to potentiation in response to tetanic stimulation, between mutant hippocampal cells (e.g. cells with presenilin-1 mutation) as compared to wild-type hippocampal cells (see entire reference). Thus in view of the teachings of Parent et al, one skilled in the art recognizes that it would require undue

experimentation to practice the claimed invention drawn to "mutant hippocampal cells having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells", since Parent et al teaches that mutant hippocampal cells do not predictably or reliably have "enhanced synaptic potentiation upon stimulation" as compared to wild-type hippocampal cells.

Further, the specification provides insufficient guidance on how to successfully practice the invention as claimed because it is further unknown to one skilled in the art what metes and bounds are envisioned by the recitation "treatment", and because no *in vivo* models are known, or adequately described, for the "treatment of Alzheimer's disease" as claimed, by which the skilled artisan could extrapolate "how to use" the invention with any reasonable expectation of success, for the reasons indicated above. Additionally, it is well accepted in the art that differences exist between *in vitro* protocols and results, e.g. *in vitro* results from studies using hippocampal slices as disclosed, versus *in vivo* protocols and results, e.g. *in vivo* studies that employ drug administration, especially as it relates to undefined parameters that do not distinguish when "treatment" is effective, or that require passage across the blood brain barrier which is impermeable to protein molecules/other molecules, or that involve undefined parameters that do not distinguish "treatment" of "Alzheimer's Disease", for example, from any different disease state. The instant specification provides insufficient guidance on how these parameters are to be determined, how a similar method was practiced in the art with a different agent or to provide even a single working *in vivo* example of the claimed methods. Additionally, it is not known at what point during any given disease state of Alzheimer's disease when "treatment" is

recommended, or how one skilled in the art knows when, or if, they have successfully practiced the instant invention; thereby, requiring undue experimentation to discover how to successfully practice Applicants' invention. Further, it is unknown, nor disclosed, what specific aspects/symptoms of claimed Alzheimer's disease are envisioned to be "treated" or what constitutes a therapeutically effective amount of claimed "candidate drug", or how to assay such *in vivo*. In other words, one skilled in the art would not reasonably be able to successfully make and use the invention, as claimed, without undue experimentation to determine such.

Claim Rejections - 35 USC § 112 second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims recite the limitation "said agent". There is insufficient antecedent basis for this limitation in the claims.

5. Claims 6 and 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "significant change" in said claims is a relative term which renders the claims indefinite. The specification does not provide a standard for ascertaining the requisite degree of change required to exactly constitute "significant change", and one skilled in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Borchelt et al (October 1997 reference; see PTO-892). Instant claim 10 is drawn to slices of mouse hippocampal cells having a mutation in a presenilin gene "combined with a candidate drug". Since Borchelt et al (see entire reference) disclose slices of mouse hippocampal cells having a mutation in a presenilin gene "combined with a candidate drug", e.g. see Figure 5 of Borchelt et al reference for disclosure of slices of mouse hippocampal cells having a mutation in a presenilin gene combined with antibodies (i.e. antibodies meet limitation of any candidate drug) specific to the C-terminus of beta-amyloid 1-40 and beta-amyloid 1-42. Thus in view of the disclosure of Borchelt et al, all limitations of claim 10 are met by the prior art. Claim 11 is a product by process claim. There is no evidence of record that the process of tetanic stimulation materially affects the product slices of mouse hippocampal cells from the product as claimed in claim 10, see in particular evidentiary support of Parent et al wherein no predictable or reliable synaptic potentiation was achieved. Thus, it appears that the products are the same and claim 11 is anticipated by Borchelt et al., as set forth above.

Status of Claims

7. No claim is allowed.

8. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
September 28, 2000

Patricia A. Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER